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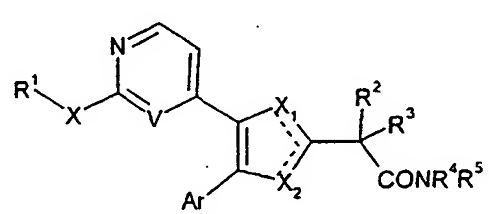
(54) Title: IMIDAZOL DERIVATIVES AS RAF KINASE INHIBITORS



(I)

(57) Abstract: Compounds of formula (I) wherein X is O, CH_2, S or NH, or the moiety X-R^1 is hydrogen; V is CH or N; R^1 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, heteroaryl, or heteroarylC_{1-6}alkyl any of which except for hydrogen may be optionally substituted; R^2 and R^3 independently represent optionally substituted C_{1-6}alkyl, or R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7}cycloalkyl or C_{3-7}cycloalkenyl ring; or R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted 5 to 7-membered heterocyclyl ring containing up to 3 heteroatoms selected from N, O, S.R^4 and R^5 independently represent hydrogen, C_{1-6} alkyl, C_{3-7}cycloalkyl, aryl, arylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl, or heterocyclylC_{1-6}alkyl, any of which except for hydrogen may be optionally substituted or R^4 and R^5 together with the nitrogen atom to which they are attached form 4- to 8-membered ring; Ar is an aryl or heteroaryl ring either of which may be optionally substituted; one of X_1 and X_2 is N and the other is NR^6, wherein R^6 is hydrogen, C_{1-6}alkyl, or arylC_{1-6}alkyl or pharmaceutically acceptable salts thereof, their use as inhibitors of Raf kinases, and pharmaceutical compositions containing them.

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IMIDAZOL DERIVATIVES AS RAF KINASE INHIBITORS

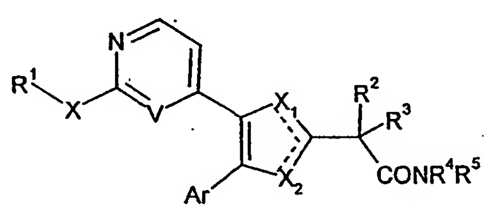
This invention rèlates to novel compounds and their use as pharmaceuticals particularly as Raf kinase inhibitors for the treatment of neurotraumatic diseases.

Raf protein kinases are key components of signal transduction pathways by which specific extracellular stimuli elicit precise cellular responses in mammalian cells. Activated cell surface receptors activate ras/rap proteins at the inner aspect of the plasmamembrane which in turn recruit and activate Raf proteins. Activated Raf proteins phosphorylate and activate the intracellular protein kinases MEK1 and MEK2. In turn, activated MEKs catalyse phosphorylation and activation of p42/p44 mitogen-activated protein kinase (MAPK). A variety of cytoplasmic and nuclear substrates of activated MAPK are known which directly or indirectly contribute to the cellular response to environmental change. Three distinct genes have been identified in mammals that encode Raf proteins; A-Raf, B-Raf and C-Raf (also known as Raf-1) and isoformic variants that result from differential splicing of mRNA are known.

Inhibitors of Raf kinases have been suggested for use in disruption of tumor cell growth and hence in the treatment of cancers, e.g. histiocytic lymphoma, lung adenocarcinoma, small cell lung cancer and pancreatic and breast carcinoma; and also in the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events, including cerebral ischemia after cardiac arrest, stroke and multi-infarct dementia and also after cerebral ischemic events such as those resulting from head injury, surgery and/or during childbirth.

We have now found a group of novel compounds that are inhibitors of Raf kinases, in particular inhibitors of B-Raf kinase.

According to the invention there is provided compounds of formula (I):



(I)

wherein

X is O, CH_2, S or NH, or the moiety X-R^1 is hydrogen;

V is CH or N;

R^1 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, heteroaryl, or heteroarylC_{1-6}alkyl any of which, except for hydrogen, may be optionally substituted;

R^2 and R^3 independently represent optionally substituted C_{1-6}alkyl, or R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7}cycloalkyl or C_{3-7}cycloalkenyl ring; or R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted 5 to 7-membered heterocyclyl ring containing up to 3 heteroatoms selected from N, O, S.

R^4 and R^5 independently represent hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl, or heterocyclylC_{1-6}alkyl, any of which, except for hydrogen, may be optionally substituted or R^4 and R^5 together with the nitrogen atom to which they are attached form 4- to 8-membered ring;

Ar is an aryl or heteroaryl ring either of which may be optionally substituted;

one of X_1 and X_2 is N and the other is NR^6, wherein R^6 is hydrogen, C_{1-6}alkyl, or arylC_{1-6}alkyl;

or pharmaceutically acceptable salts thereof.

As used herein, the double bond indicated by the dotted lines of formula (I), represent the possible tautomeric ring forms of the compounds falling within the scope of this invention, the double bond being to the unsubstituted nitrogen atom.

Alkyl and alkenyl groups referred to herein, individually or as part of larger groups e.g. alkoxy, may be straight or branched groups containing up to six carbon atoms and are optionally substituted by one or more groups selected from the group consisting of aryl, heteroaryl, heterocyclyl, C_{1-6}alkoxy, C_{1-6}alkylthio, arylC_{1-6}alkoxy, arylC_{1-6}alkylthio, amino, mono- or di-C_{1-6}alkylamino, cycloalkyl, cycloalkenyl,

carboxy and esters thereof, amide, sulphonamido, ureido, guanidino, C_{1-6}alkylguanidino, amidino, C_{1-6}alkylamidino, C_{1-6}acyloxy, azido, hydroxy, hydroxyimino and halogen. Preferably the optional substituent contains a solubilising group; suitable solubilising moieties will be apparent to those skilled in the art and include hydroxy and amine groups. Even more preferably the optional substituent include heterocyclyl, amino, mono- or di-C_{1-6}alkylamino, amide, and hydroxy or any combination thereof.

Cycloalkyl and cycloalkenyl groups referred to herein include groups having from three to seven ring carbon atoms and are optionally substituted as described hereinabove for alkyl and alkenyl groups.

When used herein, the term "aryl" includes, unless otherwise defined, single and fused rings suitably containing from 4 to 7, preferably 5 or 6, ring atoms in each ring, which rings, may each be unsubstituted or substituted by, for example, up to three substituents.

Suitable aryl groups include phenyl and naphthyl such as 1-naphthyl or 2-naphthyl.

When used herein the term "heterocyclyl" includes, unless otherwise defined, non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from O, N and S, which rings, may be unsubstituted or substituted by, for example, up to three substituents. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Examples of heterocyclyl groups include pyrrolidine, piperidine, piperazine, morpholine, imidazolidine and pyrazolidine.

When used herein, the term "heteroaryl" includes, unless otherwise defined, mono- and bicyclic heteroaromatic ring systems comprising up to four, preferably 1 or 2, heteroatoms each selected from O, N and S. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring. Examples of heteroaryl groups include pyrrole, quinoline,

isoquinoline, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole and benzimidazole.

Aryl, hererocyclyl and heteroaryl groups may be optionally substituted by preferably up to three substituents. Suitable substituents include halogen, C_{1-6}alkyl, aryl, aryl C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxy C_{1-6}alkyl, halo C_{1-6}alkyl, arylC_{1-6}alkoxy, hydroxy, nitro, cyano, azido, amino, mono- and di-*N*-C_{1-6}alkylamino, acylamino, arylcarbonylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-*N*-C_{1-6}alkylcarbamoyl, C_{1-6}alkoxycarbonyl, aryloxycarbonyl, ureido, guanidino, C_{1-6}alkylguanidino, amidino, C_{1-6}alkylamidino, sulphonylamino, aminosulphonyl, C_{1-6}alkylthio, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, heterocyclyl, heteroaryl, heterocyclyl C_{1-6}alkyl, hydroxyimino-C_{1-6}alkyl and heteroaryl C_{1-6}alkyl. Preferably the optional substituent contains a solubilising group; suitable solubilising moieties will be apparent to those skilled in the art and include hydroxy and amine groups. Even more preferably the optional substituent include heterocyclyl, amino, mono- or di-C_{1-6}alkylamino, amide, and hydroxy or any combination thereof.

X is preferably NH or X-R^1 is hydrogen and when X is NH, R^1 is preferably C_{1-6}alkyl or hydrogen.

When V is CH, X-R^1 is preferably hydrogen.

When V is N, X-R^1 is preferably NH_2.

Most preferably X-R^1 is hydrogen.

Ar is preferably an optionally substituted phenyl.

Preferred substituents for the group Ar include halo, hydroxy, hydroxy C_{1-6}alkyl, e.g. hydroxymethyl, hydroxyimino-C_{1-6}alkyl and C_{1-6}alkoxy e.g. methoxy, more preferred are halo and hydroxy. When Ar is phenyl the substituents are preferably present in the 3-position or the 3,4-positions. When Ar is phenyl it preferably has a 3-hydroxy substituent. Particular substitution patterns for Ar when phenyl are 3-hydroxy, 3-hydroxy-4-halo e.g. 3-hydroxy-4-chloro or 3-hydroxy-4-bromo, 3-hydroxy-4-methyl and 3-hydroxy-4-methoxy, more particularly 3-hydroxy-4-chloro.

R^2 and R^3 independently represent C_{1-6}alkyl or R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7}cycloalkyl or C_{3-7}cycloalkyl ring. Alternatively R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted 5 to 7-membered heterocyclyl ring containing up to 3 heteroatoms selected from N, O and S.

R^2 and R^3 preferably independently represent optionally substituted C_{1-6}alkyl, or R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7}cycloalkyl or C_{5-7}cycloalkenyl ring. More preferably R^2 and R^3 represent C_{1-6}alkyl, or R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7}cycloalkyl ring. In particular R^2 and R^3 represent methyl

Preferably R^4 and R^5 are independently hydrogen, C_{1-6}alkyl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl any of which except hydrogen may be optionally substituted or R^4 and R^5 together with the nitrogen to which they are attached from an optionally substituted 5 or 6 membered ring optionally containing up to 2 heteroatoms selected from N or O, for example morpholine, pyrrolidine or piperazine.

The compounds of formula (I) preferably have a molecular weight of less than 800.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts. It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in *J. Pharm. Sci.*, 1977, 66, 1-19, such as acid addition salts formed with

inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention.

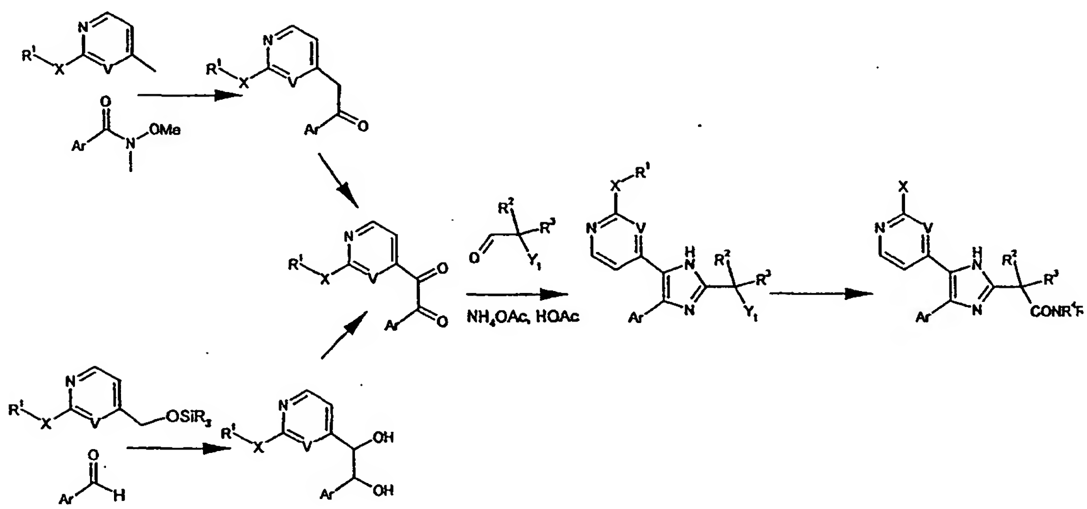
The compounds of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

The invention extends to all isomeric forms including stereoisomers and geometric isomers of the compounds of formula (I) including enantiomers and mixtures thereof e.g. racemates. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure.(% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

Compounds of formula (I) are imidazole derivatives which may be readily prepared using procedures well-known to those skilled in the art, and described in, for instance, Comprehensive Heterocyclic Chemistry, Editors Katritzky and Rees, Pergamon Press, 1984, 5, 457-497, from starting materials which are either commercially available or can be prepared from such by analogy with well-known processes. A key step in many such syntheses is the formation of the central imidazole nucleus. Suitable procedures are described in *inter alia* US Patent No's. 3,707,475 and 3,940,486 which are herein incorporated by reference in their entirety. These patents describe the synthesis of α-diketones and α-hydroxyketones

(benzoins) and their subsequent use in preparing imidazoles and N-hydroxyl imidazoles.



Preferred methods for preparing compounds of this invention are as outlined in the above scheme, wherein Y_1 is COOH or a C_{1-6} alkyl or arylC_{1-6}alkyl ester thereof. α-Diketones are prepared by condensation of the anion of, for example, a 4-substituted pyridine derivative (V = CH, R^1-X = H) with the Weinreb amide of an aryl acid or an aryl-aldehyde, followed by oxidation of the intermediate product. Heating the diketone with an aldehyde and ammonium acetate in acetic acid allows access to the imidazole nucleus. Thereafter, the group Y_1 may be converted into a group Y using conventional functional group interconversion procedures. Functional group transformations are well known in the art and are described in, for instance, *Comprehensive Organic Functional Group Transformations*, eds. A.R. Katritzky, O. Meth-Cohn, and C.W. Rees (Elsevier Science Ltd., Oxford, 1995), *Comprehensive Organic Chemistry*, eds. D. Barton and W.D. Ollis (Pergamon Press, Oxford, 1979), and *Comprehensive Organic Transformations*, R.C. Larock (VCH Publishers Inc., New York, 1989). The group Y_1 is preferably $COOCH_3$.

Non-selective alkylation of the imidazole nitrogen (using one of the procedures outlined in N. J. Liverton et al; *J. Med. Chem.*, 1999, **42**, 2180-2190) with a compound of formula L-R^6 wherein L is a leaving group, e.g. halo, sulfonate or triflate, will yield both isomers of the compounds of formula (I) where X_1 or X_2 is NR^6 in which R^6 is other than hydrogen, the isomers can be separated by chromatographic methods.

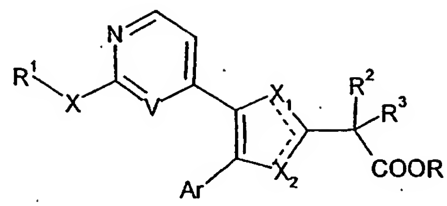
During the synthesis of the compounds of formula (I) labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example *Protective Groups in Organic Chemistry,* T.W. Greene and P.G.M. Wuts, (Wiley-Interscience, New York, 2nd edition, 1991).

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The novel carboxylic esters and the corresponding acids of formula (II) which are used as intermediates in the synthesis of the compounds of formula (I) also form part of the present invention:



(II)

wherein X, V, R^1, R^2, R^3, Ar, X_1 and X_2 are as defined for formula (I) and R is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl.

As indicated above the compounds of formula (I) and their pharmaceutically acceptable salts are useful for the treatment and/or prophylaxis of disorders in which Raf kinases, in particular B-Raf kinase, are implicated.

According to a further aspect of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as an inhibitor of B-Raf kinase.

As indicated above the compounds of formula (I) and their pharmaceutically acceptable salts are useful the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events.

According to a further aspect of the invention there is provided a method of treatment or prophylaxis of a neurotraumatic disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

According to a further aspect of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by a neurotraumatic event.

Neurotraumatic diseases/events as defined herein include both open or penetrating head trauma, such as caused by surgery, or a closed head trauma injury, such as caused by an injury to the head region. Also included within this definition is ischemic stroke, particularly to the brain area, transient ischemic attacks following coronary by-pass and cognitive decline following other transient ischemic conditions.

Ischemic stroke may be defined as a focal neurologic disorder that results from insufficient blood supply to a particular brain area, usually as a consequence of an embolus, thrombi, or local atheromatous closure of the blood vessel. Roles for stress stimuli (such as anoxia), redox injury, excessive neuronal excitatory stimulation and inflammatory cytokines in this area has been emerging and the present invention provides a means for the potential treatment of these injuries. Relatively little treatment, for an acute injury such as these has been available.

The compounds of the invention may also be used in the treatment or prophylaxis of cancers.

The compounds of the invention may also be of use for the treatment or prophylaxis of CSBP/p38 mediated diseases as described in WO 99/01131 and WO 99/01130.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of formula (I) may conveniently be administered by any of the routes conventionally used for drug administration, for instance, parenterally, orally, topically or by inhalation. The compounds of formula (I) may be administered in conventional dosage forms prepared by combining it with standard pharmaceutical carriers according to conventional procedures. The compounds of formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the

pharmaceutically acceptable carrier is dictated by the amount of compound of formula (I) with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule or nonaqueous liquid suspension.

The compounds of formula (I) are preferably administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The intravenous form of parenteral administration is generally preferred. The compounds may be administered as a bolus or continuous infusion e.g. over 3 days. Appropriate dosage forms for such administration may be prepared by conventional techniques.

The compounds of formula (I) may also be administered orally. Appropriate dosage forms for such administration may be prepared by conventional techniques.

The compounds of formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as aerosol formulations, may be prepared by conventional techniques.

The compounds of formula (I) may also be administered topically, that is by non-systemic administration. This includes the application of the inhibitors externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream.

For all methods of use disclosed herein the daily oral dosage regimen will preferably be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5mg to 15mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of the inhibitors will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the inhibitors given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests. In the case of pharmaceutically acceptable salts the above figures are calculated as the parent compound of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention and the following Descriptions illustrate the preparation of intermediates used in the preparation of these compounds.

Abbreviations used herein are as follows-

THF means tetrahydrofuran.

Description 1: 2-[4-(4-Chloro-3-methoxyphenyl)-5-pyridin-4-yl-1*H*-imidazol-2-yl]-2-methyl propionic acid methyl ester

Step 1. 4-Chloro-3,*N*-dimethoxy-*N*-methyl-benzamide

A suspension of 4-chloro-3-methoxybenzoic acid (F. Claudi *et al J. Med. Chem.*, 1992, 35, 4408) (37.2g, 0.2mol) in dichloromethane (500ml) containing oxalyl chloride (26ml) was treated with *N,N*-dimethylformamide (10 drops). After stirring at room temperature for 6 hours the solution was concentrated at reduced pressure, additional dichloromethane was added to the residue and the solvent was re-evaporated. The residue was dissolved in acetonitrile (600ml) and methoxymethylamine hydrochloride (20.5g, 0.21mol) added. The mixture was cooled in an ice-bath, a solution of pyridine (80ml) in acetonitrile (150ml) added dropwise, and the mixture stirred at room temperature for 18 hours. The solution was concentrated and the residue partitioned between ethyl acetate and saturated potassium carbonate solution. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure to give the title compound (40.0g, 87%) as a colourless oil; MS(ES+) m/e 230/232 $[M+H]^+$.

Step 2. 1-(4-Chloro-3-methoxy-phenyl)-2-pyridin-4-yl-ethanone

4-Picoline (16.9ml, 0.174mol) was added dropwise to a stirred solution of lithium di-isopropylamide (110ml, 0.22mol, 2M solution in heptane, ethylbenzene, tetrahydrofuran) in dry tetrahydrofuran (150ml) at -78°C. After stirring at -78°C for 15 minutes a solution of the product of Step 1 (40.0g, 0.174mol) in tetrahydrofuran (100ml) was added dropwise. The reaction was allowed to warm to room temperature over 3 hours. The solution was cooled in ice and saturated ammonium chloride solution was added. The aqueous mixture was extracted with ethyl acetate, washed with brine, dried ($MgSO_4$), filtered and concentrated at reduced pressure. The resulting gum was triturated with cold diethyl ether/hexane (1:1, 300ml) and the

solid collected to give the title compound, as a pale yellow solid (29g, 64%); MS(ES+) m/e 262/264 $[M+H]^+$.

Step 3. 1-(4-Chloro-3-methoxy-phenyl)-2-pyridin-4-yl)-ethane-1,2-dione

A solution of the product of Step 2 (22.5g, 86mmol) in dimethylsulphoxide (150ml) was stirred at 55°C. Hydrogen bromide (48% aqueous, 21ml) was added dropwise and the solution maintained at 55°C for 1 hour. After cooling to room temperature, the solution was poured into a solution of sodium acetate (21g) in ice-water (1 litre) and the resulting slurry was stirred at room temperature for 30 minutes. The mixture was extracted with ethyl acetate and the organic layers were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated at reduced pressure. The residue was triturated with diethyl ether/hexane (1:4) and the solid collected to give the title compound as a yellow solid; MS(EI) m/e 275/277 $[M^{\cdot}]^+$.

Step 4. 2-[4-(4-Chloro-3-methoxyphenyl)-5-pyridin-4-yl-1*H*-imidazol-2-yl]-2-methyl propionic acid methyl ester

The product of Step 3 (11.03g, 40mmol), 2,2-dimethyl-3-*oxo*-propionic acid methyl ester (6.77g, 52mmol) and ammonium acetate (30.8g, 400mmol) were heated at 100°C in acetic acid (100ml) for 1 hour. The solution was concentrated under reduced pressure and the residue poured on to ice:0.880 ammonia solution. The solution was extracted with ethyl acetate, washed with water and brine, dried ($MgSO_4$) and evaporated to a solid. The solid was triturated with hexane, filtered and dried to afford the title compound (11.02g, 71%) as a tan solid; MS(AP+) m/e 386/388 $[M+H]^+$.

Description 2: 2-[4-(4-Chloro-3-methoxyphenyl)-5-pyridin-4-yl-1*H*-imidazole-2-yl]-2-methyl-propionic acid

The product of D1 (11.03g, 28mmol) was suspended in methanol (150ml), 2M sodium hydroxide solution (42ml, 84mmol) added and the mixture warmed to 50°C for 3 hours. After concentration at reduced pressure, the residue was dissolved in water, washed with ethyl acetate and then acidified to pH 4-5 with acetic acid. The resulting white precipitate was filtered, washed with water and dried over

phosphorous pentoxide at reduced pressure to afford the title compound (7.75g, 74%) as a lemon solid; MS(AP+) m/e 372/374 $[M+H]^+$.

Description 3: 2-[4-(3,4-Dichlorophenyl)-5-pryidin-4-yl-1*H*-imidazole-2-yl]-2-methyl-propionic acid

Step 1. 1-(3,4-Dichlorophenyl)-2-pyridin-4-yl-ethane-1,2-diol

4-(*tert*-Butyldimethylsilyloxymethyl)-pyridine (T. F. Gallagher *et al, Bioorganic and Medicinal Chemistry;* 1997, 5, 49) (67g, 0.3mol) was dissolved in THF (250ml) and cooled to -40°C. The solution was treated with a 2M solution of lithuim diisopropylamide in THF (200ml, 0.4mol) and stirred for 45 minutes maintaining a temperature of -40 to -20°C, before the dropwise addition of 3,4-dichlorobenzaldehyde (55.13g, 0.32mol) in THF (250ml). The mixture was allowed to warm to room temperature then stirred for a further 18 hours. After re-cooling to 0°C the reaction was quenched with saturated ammonium chloride solution (500ml), and the resulting two phase mixture separated. The aqueous phase was extracted with ethyl acetate and the combined organics concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate solution, water and brine, dried ($MgSO_4$) and concentrated under reduced pressure to an oil (129g). The oil was dissolved in THF (300ml) and a 1M solution of tetrabutylammonium fluoride (360ml, 0.36mol) added dropwise. The solution was stirred at room temperature for 45 minutes, then concentrated to an oil under reduced pressure. The oil was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution, water and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The oil was triturated with hexane and the resulting solid filtered and washed with hexane to afford the title compound (67.58g 79%) as a tan solid; MS(AP+) m/e 284/286/288 $[M+H]^+$.

Step 2. 1-(3,4-Dichlorophenyl)-2-pyridin-4-yl-ethane-1,2-dione

Dimethylsulfoxide (37ml, 0.53mol) was dissolved in dichloromethane (250ml) and cooled to –78°C. Oxalyl chloride (34.5ml, 0.40mol) was added dropwise and the solution stirred for 20 min. A solution of the product of Step 1 (34g, 0.12mol) in

dimethylsulfoxide (40ml) and dichloromethane (200ml) was added dropwise at –78°C, and the solution stirred for 30 minutes. Triethylamine (104ml, 0.74mol) was added dropwise and the solution became floculent such that overhead stirring became necessary. The solution was allowed to stir at room temperature over 2 hours then was poured on to ice/saturated sodium bicarbonate solution. The aqueous layer was separated, and re-extracted with dichloromethane. The combined organic phases were concentrated under reduced pressure to a green-yellow solid. The solid was redissolved in dichloromethane and washed with water and brine, dried ($MgSO_4$) and evaporated to a solid. The crude solid was purified by silica gel chromatography eluting with dichloromethane, to afford the title compound (28.6g, 85%) as a yellow solid; MS(-ve ion) m/e 279/281/283 $[M-H]^-$.

Step 3. 2-[4-(3,4-Dichlorophenyl)-5-pyridin-4-yl-1*H*-imidazol-2-yl]-2-methyl propionic acid methyl ester

The product of Step 2 (5.60g, 20mmol) was reacted with 2,2-dimethyl-3-oxo-propionic acid methyl ester (3.38g, 26mmol) and ammonium acetate (15.4g, 200mmol) as described in Description 1, Step 4 to afford the title compound (5.06g, 65%) as a tan solid; MS(AP+) m/e 391/393/395 $[M+H]^+$.

Step 4. 2-[4-(3,4-Dichlorophenyl)-5-pryidin-4-yl-1*H*-imidazole-2-yl]-2-methyl-propionic acid

The product of Step 3 (5.26g, 14mmol) was reacted with 2M sodium hydroxide solution (20ml, 40mmol) in methanol as described in Description 2, to afford the title compound (2.36g, 45%) as a beige solid; MS(AP+) m/e 376/378/380 $[M+H]^+$.

Example 1: *n*-Butyl-2-[4-(4-chloro-3-methoxyphenyl)-5-pyridin-4-yl-1*H*-imidazole-2-yl] isobutylamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (63mg, 0.33mmol) and 1-hydroxybenzotriazole hydrate (41mg, 0.3mmol) were added to a suspension of the product of Description 2 (111mg, 0.3mmol) in dichloromethane (5ml). The mixture was stirred at room temperature until a clear yellow solution was obtained then *n*-butylamine (0.022ml, 0.3mmol) added. The solution was stirred at room

temperature overnight then evaporated under reduced pressure to a solid. The solid was dissolved in ethyl acetate, washed with saturated sodium bicarbonate solution, water and brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound (113mg, 88%) as a cream solid; MS(AP-) m/e 425/427 $[M-H]^-$.

Example 2: *n*-Butyl-2-[4-(4-chloro-3-hydroxyphenyl)-5-pyridin-4-yl-1*H*-imidazole-2-yl]isobutylamide

The product of Example 1 (130mg, 0.3mmol) was dissolved in dichloromethane (5ml) cooled to 0°C, then treated dropwise with 1M solution of boron tribromide in dichloromethane (1.2ml, 1.2mmol). After stirring at room temperature for 18 hours, the heterogeneous mixture was diluted with dichloromethane (10ml), 2M hydrochloric acid (1 ml) added and the mixture heated at reflux for 30 min. After cooling to room temperature, the solution was basified with saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound (101mg, 82%) as yellow powder; MS(AP-) m/e 411/413 $[M-H]^-$.

Example 3: 2-[4-(3,4-Dichlorophenyl)-5-pyridin-4-yl-1*H*-imidazol-2-yl]-2-methyl-1-morpholin-4-yl-propan-1-one

The product of Description 3 (113mg, 0.3mmol) was reacted with morpholine (0.027ml, 0.3mmol) as described in Example 1 to afford the title compound (66mg, 49%) as a cream solid; MS(AP+) m/e 445/447/449 $[M+H]^+$.

The following examples were prepared from the product of Description 2 by the general method described in Example 1.

Example	Amine	Characterisation

4	2-[4-(4-Chloro-3-methoxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-2-methyl-1-pyrrolidin-1-yl-propan-1-one	Pyrrolidine	MS(AP+) m/e 426/428 $[M+H]^+$
5	2-[4-(4-Chloro-3-methoxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-N-(tetrahydro-furan-2-ylmethyl)-isobutyramide	Tetrahydro furfurylamine	MS(AP+) m/e 455/457 $[M+H]^+$
6	2-[4-(4-Chloro-3-methoxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-2-methyl-1-(4-methyl-piperazin-1-yl)-propan-1-one	*N*-methyl-piperazine	MS(AP+) m/e 454/456 $[M+H]^+$
7	*N*-(2-Acetylamino-ethyl)-2-[4-(4-chloro-3-methoxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-isobutyramide	*N*-acetyl ethylene diamine	MS(AP+) m/e 455/457 $[M+H]^+$
8	2-[4-(4-Chloro-3-methoxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-*N*-pyridin-3-ylmethyl-isobutyramide	3-(Aminomethyl) pyridine	MS(AP+) m/e 462/464 $[M+H]^+$
9	2-[4-(4-Chloro-3-methoxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-*N*-cyclopropyl-isobutyramide	Cyclopropylamine	MS(AP+) m/e 411/413 $[M+H]^+$
10	2-[4-(4-Chloro-3-methoxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-*N*-(2-methoxy-ethyl)-isobutyramide	2-Methoxy ethylamine	MS(AP+) m/e 429/431 $[M+H]^+$

The following examples were prepared by the general method described in Example 2.

Example		**Precursor**	**Characterisation**
11	2-[4-(4-Chloro-3-hydroxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-2-methyl-1-pyrrolidin-1-yl-propan-1-one	Example 4	MS(AP+) m/e 412/414 $[M+H]^+$

12	2-[4-(4-Chloro-3-hydroxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-N-(tetrahydro-furan-2-ylmethyl)-isobutyramide	Example 5	MS(AP+) m/e 441/443 $[M+H]^+$
13	2-[4-(4-Chloro-3-hydroxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-2-methyl-1-(4-methyl-piperazin-1-yl)-propan-1-one	Example 6	MS(AP+) m/e 440/442 $[M+H]^+$
14	*N*-(2-Acetylamino-ethyl)-2-[4-(4-chloro-3-hydroxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-isobutyramide	Example 7	MS(AP+) m/e 441/443 $[M+H]^+$
15	2-[4-(4-Chloro-3-hydroxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-*N*-pyridin-3-ylmethyl-isobutyramide	Example 8	MS(AP+) m/e 448/450 $[M+H]^+$
16	2-[4-(4-Chloro-3-hydroxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-*N*-cyclopropyl-isobutyramide	Example 9	MS(AP+) m/e 397/399 $[M+H]^+$
17	2-[4-(4-Chloro-3-hydroxy-phenyl)-5-pyridin-4-yl-1H-imidazol-2-yl]-*N*-(2-methoxy-ethyl)-isobutyramide	Example 10	MS(AP+) m/e 415/417 $[M+H]^+$

It is to be understood that the present invention covers all combinations of particular and preferred sub groups described hereinabove.

BIOLOGICAL EXAMPLES

The activity of compounds of formula (I) as B-Raf inhibitors may be determined by the following *in vitro* assay:

Raf Kinase assay

Activity of human recombinant B-Raf protein was assessed in vitro by assay of the incorporation of radiolabelled phosphate to recombinant MAP kinase (MEK),

a known physiologic substrate of B-Raf. Catalytically active human recombinant B-Raf protein was obtained by purification from sf9 insect cells infected with a human B-Raf recombinant baculovirus expression vector. To ensure that all substrate phosphorylation resulted from B-Raf activity, a catalytically inactive form of MEK was utilised. This protein was purified from bacterial cells expression mutant inactive MEK as a fusion protein with glutathione-S-transferase (GST-kdMEK).

Method: Standard assay conditions of B-Raf catalytic activity utilised 3ug of GST-kdMEK, 10uM ATP and 2uCi ^{33}P-ATP, 50mM MOPS, 0.1mM EDTA, 0.1M sucrose, 10mM $MgCl_2$ plus 0.1% dimethylsulphoxide (containing compound where appropriate) in a total reaction volume of 30ul. Reactions were incubated at 25°C for 90 minutes and reactions terminated by addition of EDTA to a final concentration of 50uM. 10ul of reaction was spotted to P30 phosphocellulose paper and air dried. Following four washes in ice cold 10% trichloroacetic acid, 0.5% phosphoric acid, papers were air dried prior to addition of liquid scintillant and measurement of radioactvity in a scintillation counter.

Results: The compounds of the examples were found to be effective in inhibiting B-Raf mediated phosphorylation of GST-kdMEK substrate having IC_{50}'s of < 3 μM.

The activity of compounds as Raf inhibitors may also be determined by the assays described in WO 99/10325; McDonald, O.B., Chen, W.J., Ellis, B., Hoffman, C., Overton, L., Rink, M., Smith, A., Marshall, C.J. and Wood, E.R. (1999) A scintillation proximity assay for the Raf/MEK/ERK kinase cascade: high throughput screening and identification of selective enzyme inhibitors, Anal. Biochem. 268: 318-329 and AACR meeting New Orleans 1998 Poster 3793.

The neuroprotective properties of B-Raf inhibitors may be determined by the following *in vitro* assay:

Neuroprotective properties of B-Raf inhibitors in rat hippocampal slice cultures

Organotypic cultures provide an intermediate between dissociated neuronal cell cultures and *in-vivo* models of oxygen and glucose deprivation (OGD). The majority of glial-neuronal interactions and neuronal circuitry are maintained in cultured hippocampal slices, so facilitating investigation of the patterns of death among differing cell types in a model that resembles the *in vivo* situation. These cultures allow the study of delayed cellular damage and death 24 hours, or more, post-insult and permit assessment of the consequences of long-term alterations in culture conditions. A number of laboratories have reported delayed neuronal damage in response to OGD in organotypic cultures of the hippocampus (Vornov *et al.*, *Stroke*, 1994, 25, 57-465; Newell *et al.*, *Brain Res.*, 1995, 676, 38-44). Several classes of compounds have been shown to protect in this model, including EAA antagonists (Strasser *et al.*, *Brain Res.*, 1995, 687, 167-174), Na channel blockers (Tasker *et al.*, *J. Neurosci.*, 1992, 12, 98-4308) and Ca channel blockers (Pringle *et al.*, *Stroke*, 1996, 7, 2124-2130). To date, relatively little is known of the roles of intracellular kinase mediated signalling pathways in neuronal cell death in this model.

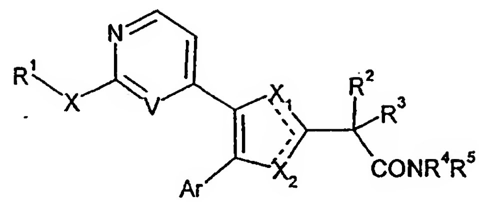
Method: Organotypic hippocampal slice cultures were prepared using the method of Stoppini *et al.*, *J. Neurosci. Methods*, 1995, 37, 173-182. Briefly, 400 micron sections prepared from hippocampi of 7-8 day postnatal Sprague Dawley rats are cultured on semiporous membranes for 9-12 days. OGD is then induced by incubation in serum and glucose-free medium in an anaerobic chamber for 45 minutes. Cultures are then returned to the air / CO_2 incubator for 23 hours before analysis. Propidium iodide (PI) is used as an indicator of cell death. PI is non toxic to neurones and has been used in many studies to ascertain cell viability. In damaged neurons PI enters and binds to nucleic acids. Bound PI shows increased emission at 635nm when excited at 540nm. One PI fluorescence image and one white light image are taken and the proportion of cell death analysed. The area of region CA1 is defined from the white light image and superimposed over the PI

image. The PI signal is thresholded and area of PI damage expressed as a percentage of the CA1 area. Correlation between PI fluorescence and histologically confirmed cell death has been validated previously by Nissl-staining using cresyl fast violet (Newell *et al.*, *J. Neurosci.*, 1995, 15, 7702-7711).

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

Claims:

1. A compound of formula (I):



(I)

wherein

X is O, CH_2, S or NH, or the moiety X-R^1 is hydrogen;

V is CH or N;

R^1 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylC_{1-6}alkyl, heterocyclyl, heterocyclylC_{1-6}alkyl, heteroaryl, or heteroarylC_{1-6}alkyl any of which except for hydrogen may be optionally substituted;

R^2 and R^3 independently represent optionally substituted C_{1-6}alkyl, or R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7}cycloalkyl or C_{3-7}cycloalkenyl ring, or R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted 5 to 7-membered heterocyclyl ring containing up to 3 heteroatoms selected from N, O, and S; R^4 and R^5 independently represent hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, arylC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl, or heterocyclylC_{1-6}alkyl, any of which, except for hydrogen, may be optionally substituted, or R^4 and R^5 together with the nitrogen atom to which they are attached form 4- to 8-membered ring;

Ar is an aryl or heteroaryl ring either of which may be optionally substituted;

one of X_1 and X_2 is N and the other is NR^6, wherein R^6 is hydrogen, C_{1-6}alkyl, or arylC_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein X-R^1 is hydrogen.

3. A compound according to any one of the preceding claims wherein Ar is phenyl.

4. A compound according to claim 3 wherein Ar is substituted by up to 3 substituents independently selected from halo, hydroxy, hydroxy C_{1-6}alkyl, hydroxyimino C_{1-6}alkyl, and C_{1-6}alkoxy.

5. A compound as claimed in any preceding claim wherein R^2 and R^3 represent C_{1-6}alkyl, or R^2 and R^3 together with the carbon atom to which they are attached form an optionally substituted C_{3-7}cycloalkyl ring.

6. A compound as claimed in any preceding claim wherein R^4 and R^5 are independently hydrogen, C_{1-6}alkyl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl any of which except hydrogen may be optionally substituted, or R^4 and R^5 together with the nitrogen to which they are attached form an optionally substituted 5 or 6 membered ring optionally containing up to 2 heteroatoms selected from N or O.

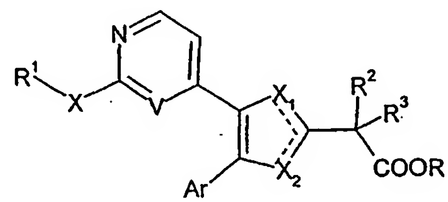
7. A compound as described in the Examples.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

9. The use of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by a neurotraumatic event.

10. The use of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the prophylactic or therapeutic treatment of cancer.

11. A compound of formula (II):



(II)

wherein X, V, R^1, R^2, R^3, Ar, X_1 and X_2 are as defined for formula (I) and R is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl.

INTERNATIONAL SEARCH REPORT

Inte   al Application No
PCT/GB 01/00908

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 C07D401/14 C07D405/14 A61K31/44 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 12876 A (MERCK & CO INC ;SELNICK HAROLD G (US); CLAREMON DAVID A (US); LIVE) 10 April 1997 (1997-04-10) page 1 -page 3; claim 21	1-11
A	GB 2 306 108 A (MERCK & CO INC) 30 April 1997 (1997-04-30) page 1 -page 2; claim 1	1-11
X	US 4 447 431 A (SALLMANN, ALFRED) 8 May 1984 (1984-05-08) claim 13	11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 May 2001	25/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I

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